Cardiovascular responses during histamine iontophoresis therapy

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The primary purpose of this study was to determine the effect of histamine iontophoresis on the cardiovascular system. Blood pressure and heart rate were monitored in 15 healthy males (ages 23-28 years) during histamine iontophoresis and direct current stimulation treatments. Cardiovascular responses were monitored before (for five minutes), during (for 20 minutes) and after (for five minutes) treatments. Blood pressure and heart rate did not change significantly ($p > 0.05$) from the baseline during either of the treatments, except in the fifth minute of the treatment when the systolic blood pressure during histamine iontophoresis was significantly lower than during direct current stimulation ($p < 0.01$). No other significant difference in the measured responses was noted. It was concluded that local administration of histamine dihydrochloride (1 per cent gel) into the skin by direct current for 20 minutes did not appreciably alter the blood pressure and heart rate responses.

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The use of iontophoresis in physical therapy is not new; however, there is a renewed interest in its clinical application around the world. The physical therapy profession often looks upon iontophoresis with some degree of possessiveness, but recently other medical specialists have shown increased interest in the procedure (La Forest 1984). Over the years, histamine iontophoresis has been usually recommended in the treatment of peripheral indolent ulcers (Harris 1967, Kovacs 1958, Nelson and Currier 1987). This recommendation is based on the premise that when absorbed, histamine causes arterial vasodilatation and increased capillary permeability. The known untoward reactions associated with intramuscularly administered histamine include a fall in blood pressure, an increase in heart rate, sweating and flushing of the skin (Harris 1967, Hayes 1979, Nelson and Currier 1987). The techniques of ionic transfer is recommended by many physical agent text books (Boone 1981, Cummings 1987, Harris 1967, Kahn 1983, Kovacs 1958, Nelson and Currier 1987, Shriber 1975) but to date few studies have systematically investigated the acute effects of histamine iontophoresis treatment on the cardiovascular system.

Abramson et al (1967) evaluated the effectiveness of histamine iontophoresis in the treatment of chronic leg ulcers. Fresh solution of histamine diphosphate (1:10,000 concentration) was used and after four months of treatment, the procedure enhanced the healing of the indolent wounds. The common side effects reported included headache, dizziness, lightheadness, local itching and swelling. These untoward reactions suggest a perturbation of the cardiovascular system. However, there is a dearth of clinical data on the blood pressure and heart rate responses during histamine iontophoresis. Because patients with peripheral vascular disease, rheumatic arthritis or recalcitrant ulcers which may benefit from histamine iontophoresis therapy may also have an underlying cardiorespiratory disease, it is important to investigate the cardiovascular response during histamine iontophoresis treatment.

Simple, noninvasive measures of cardiovascular response include heart rate, systolic and diastolic blood pressures (Kispert 1987). Previous studies have monitored the local blood flow and oxygen consumption during histamine iontophoresis (Abramson et al 1967), but no known previous study has monitored the blood pressure and heart rate responses.

Therefore, the purpose of this study was to determine the blood pressure and heart rate responses during histamine iontophoresis treatment in healthy subjects. A significant fall in blood pressure and heart rate during the treatment as a sequel to the perturbation of the cardiovascular system was expected.

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Methods

Prior to commence of the study, the experimental protocol was approved by the Human Ethics Committee of Obafemi Awolowo University.

Subjects

Fifteen undergraduate male students served as subjects. Informed consent was obtained from each. None of the subjects had any previous history of asthma, had fever or any known sensitivity reaction to histamine. Average age of the subjects was 25.5 years (sd = ± 1.5 years, range 23 - 28 years), average height was 169.0 cm (sd = ± 5.3 cm, range = 163 - 178 cm) and the average weight was 57.5 kg (sd = ± 8.7 kg, range = 48 - 84 kg).

Experimental design

A quasi-experimental (time series) design (Currier 1981) was adopted in this study, since the primary aim was to compare cardiovascular responses during histamine ionic transfer with responses during direct current (control) treatment at different time frames. Each subject acted as their own control, and cardiovascular responses were monitored periodically under two experimental (ie, histamine iontophoresis and direct current stimulation) conditions. Cardiovascular responses were recorded before, during and after each treatment. The treatments were administered on different days but within a one week interval. The order of presentation of the experimental conditions were randomised. All subjects were blind to the pharmacological composition of the gel.

The subjects were instructed not to eat, smoke cigarettes or drink beverages containing caffeine at least six hours prior to data collection, and not to engage in rigorous physical activities one day before the study. Participants wore non-restrictive clothing during data collection.

Instrumentation

The subjects' height and weight were measured with a stadiometer (Seca, Prazision Furdie, Gesundheit, West Germany). Blood pressure was monitored over the brachial artery by an automated blood pressure and heart rate monitoring system (Micronta ® Ritter Tycos, Division of Sybron Corp, Route 1, Box 1, Arden, NC 28704). The bladder of the Micronta ® device contains an electronic infrasonic transducer that monitors the pulse rate and blood pressure simultaneously and displays them on a screen. The instrument is a versatile device designed for research purposes and clinical work. In a pilot project, good agreement ($r = 0.90$; $p < 0.01$) was recorded between the readings of the automated electronic device and measurements taken with the conventional mercury sphygmomanometer. A stopwatch was employed to monitor the treatment duration.

The histamine gel (1:100 concentration) used in this study was prepared by a pharmacist (E.O.A.). The dosage (1 per cent gel) employed is in conformity with Hayes (1979) recommendation . The gel contained 1 per cent histamine dihydrochloride, 45 per cent bentonite, 15 per cent glycerine and 39 per cent water. A Preston ® galvanic current stimulator (J.A. Preston Corporation, 60 Page Road, Clifton, NJ 07012) was used to introduce the histamine ion into the subjects' tissue.

Procedure

On arrival in the laboratory, the subjects' height and weight were measured. Subsequently, participants were instructed to lie supine on a plinth and a pillow was placed under both knees to aid relaxation. Each subject was in the supine resting position for 25 minutes. This was followed by 20 minutes of either histamine iontophoresis or direct current stimulation (control) treatments.

The treatment protocol described by Balogun et al (1990) was adopted. Specifically, histamine gel was evenly applied over the middle of the right quadriceps femoris muscle (measuring 5 cm x 5 cm) using a wooden spatula. The electrodes of the stimulator were padded with eight layers of towel moistened in water. The active (anode) electrode was placed over the gel and the dispersive (cathode) electrode was placed below the right patella. Both electrodes were held in place with a velcro strap covering the entire electrode area to ensure even distribution of pressure. The active and dispersive electrode were connected to the positive and negative polarity of the stimulator, respectively. The same protocol was followed during the direct current stimulation condition except that the histamine gel was not applied to the quadriceps femoris muscle. With the electrodes in place, the current intensity was gradually increased and the subjects were instructed to indicate immediately they started to experience a tingling sensation under the electrode. For each subject, the current intensity (mA) was maintained at the sensory threshold during treatment (Hayes 1979). The subjects' sensory thresholds ranged between six and 13 mA.

The baseline blood pressure and heart rate were measured after 20 minutes in the supine (resting) position and at the end of the 25th minute of rest. During the treatment phase, the cardiovascular responses were monitored in every fifth minute of the 20 minute treatment period. Following the treatment, and still in a supine lying position, the subjects' cardiovascular responses were also monitored at the end of the first minute and at the end of the fifth minute of recovery. Immediately and 24 hours post treatment, subjects were asked if they had experienced any "unusual local and general side effects as a result of the treatment".

Data Analysis

For each subject, the mean cardiovascular response at rest and during the treatment phase was calculated. A paired dependent t - test with Boneferroni correction was used for multiple comparison to determine if there was a significant

difference in the cardiovascular responses between the baseline (supine resting) response and the response during each treatment. Furthermore, a paired *t*- test was employed to compare the cardiovascular responses (at each time frame) between the two experimental conditions. A p value of less than 0.05 was considered statistically significant.

Results

Presented in Table 1 are the results of the paired t -test analysis comparing the baseline (supine resting) cardiovascular response with responses during treatment. No significant difference ($p > 0.05$) was obtained between the mean resting cardiovascular response and the mean response during histamine iontophoresis and direct current stimulation treatments.

The cardiovascular responses during the different phases of the experimental conditions are presented in Tables 2 to 4. Following histamine iontophoresis, there was a gradual fall in systolic blood pressure (Table 2). At the fifth minute of treatment, the decrease in systolic blood pressure during histamine iontophoresis was significantly ($t = 3.50, p < 0.01$) lower than the response during direct current stimulation. No other comparison was statistically significant (Table 2).

In the treatment phase, the diastolic blood pressure during histamine iontophoresis was consistently higher than the response throughout the direct current stimulation (Table 3). However, the differences are not statistically significant. The heart rate responses during both treatments are presented in Table 4. During the three experimental (ie resting, treatment and recovery) phases, no significant difference was obtained in the heart rate between the histamine iontophoresis and direct current stimulation treatments.

None of the subjects had any major complaint or untoward reaction during and following the direct current stimulation treatment. However, some

Table 1.
Changes in the cardiovascular system following histamine iontophoresis and direct current stimulation treatments.

Variables	Supine (resting) phase	Treatment phase	*t*-value
	Mean ± SD	Mean ± SD	
Histamine iontophoresis treatment			
Systolic blood pressure (mm Hg)	101.5 ± 6.1	100.5 ± 6.9	0.420
Diastolic blood pressure (mm Hg)	66.6 ± 6.9	69.3 ± 7.2	1.038
Heart rate (beats.min^{-1})	61.9 ± 7.6	61.9 ± 9.9	0.021
Direct current stimulation treatment			
Systolic blood pressure (mm Hg)	100.3 ± 7.0	101.2 ± 7.1	0.336
Diastolic blood pressure (mm Hg)	67.3 ± 8.2	68.3 ± 6.3	0.350
Heart rate (beats .min^{-1})	63.0 ± 9.7	63.6 ± 8.9	0.000

SD = Standard deviation
* $p>0.05$

Table 2.
The systolic blood pressure (mm Hg) response at different time frames during histamine iontophoresis and direct current stimulation treatments.

Time frame	Histamine iontohoresis	Direct current stimulation	*t*-value
	Mean±SD	Mean±SD	
Resting phase			
1st minute	100.2 ± 7.1	99.3 ± 7.7	1.16
5th minute	101.9 ± 5.3	100.3 ± 7.8	1.20
Treatment phase			
1st minute	102.3 ± 6.6	102.1 ± 7.3	0.11
5th minute	99.9 ± 6.8	102.9 ± 6.8	-3.50*
10th minute	98.5 ± 8.2	99.6 ± 8.1	-0.65
15th minute	102.1 ± 8.0	100.6 ± 9.3	0.73
20th minute	100.5 ± 8.1	100.7 ± 7.3	-0.17
Recovery phase			
1st minute	99.7 ± 7.1	99.2 ± 7.6	0.40
5th minute	100.9 ± 7.7	99.1 ± 6.9	1.54

*p <0.01

Table 3.
The diastolic blood pressure (mm Hg) response at different time frames during histamine iontophoresis and direct current stimulation treatments.

Time frame	Histamine iontophoresis	Direct current stimulation	*t*-value
	Mean±SD	Mean±SD	
Resting phase			
1st minute	66.5 ± 6.7	66.5 ± 9.2	0.00
5th minute	66.3 ± 7.5	67.7 ± 8.3	-0.81
Treatment phase			
1st minute	69.9 ± 6.2	68.9 ± 8.3	0.64
5th minute	69.2 ± 7.8	68.6 ± 5.5	0.36
10th minute	69.4 ± 7.6	68.0 ± 8.2	0.88
15th minute	70.5 ± 8.3	68.5 ± 6.3	0.97
20th minute	68.5 ± 8.4	67.6 ± 6.2	0.40
Recovery phase			
1st minute	69.4 ± 8.1	70.5 ± 6.0	-0.65
5th minute	68.6 ± 7.0	68.2 ± 6.1	0.20

*p <0.05

Table 4.
The heart rate (beats.min^{-1}) response at different time frames during histamine iontophoresis and direct current stimulation treatments.

Time frame	Histamine iontophoresis	Direct current stimulation	*t*-value
	Mean±SD	Mean ±SD	
Resting phase			
1st minute	62.9 ± 8.2	64.5 ± 12.9	-0.60
5th minute	60.3 ± 7.2	63.3 ± 9.3	-1.25
Treatment phase			
1st minute	63.3 ± 12.3	65.3 ± 13.2	-0.58
5th minute	62.2 ± 7.9	65.6 ± 9.7	-1.53
10th minute	62.9 ± 9.9	63.2 ± 10.3	-0.26
15th minute	63.1 ± 11.2	62.7 ± 7.9	0.14
20th minute	61.5 ± 8.4	61.2 ± 7.9	0.15
Recovery phase			
1st minute	63.3 ± 10.8	60.8 ± 7.9	1.02
5th minute	61.1 ± 9.3	60.6 ± 8.1	0.24

*p <0.05

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of the subjects experienced discomfort or some after effects following histamine iontophoresis treatment. The untoward reactions are summarised in Table 5. All the subjects complained of burning or tingling sensation under the two electrodes during treatment. The burning sensation was relieved by wetting the pad. Immediately following the treatment, one (6.7 per cent) subject experienced dizziness, and one minor headache, while two (12.4 per cent) subjects complained of "heaviness of the lower extremities". Twenty-four hours post treatment, one (6.7 per cent) subject had minor scalding under the active electrode; seven (46.7 per cent) subjects reported itching under the active elecrode and four (26.8 per cent) subjects experienced weals under the active electrode.

Discussion

The primary objective of this study was to determine the effect of histamine iontophoresis on the cardiovascular system. Studies of this nature are needed as physiotherapists are often not sensitive to potential physiological stresses imposed by physiotherapeutic modalities on either the healthy or the compromised cardiovascular system. The direct current stimulation experimental condition was included in the study design to delineate the additive influence of electrical stimulation required during histamine ionic transfer. The overall blood pressure and heart rate did not change significantly from the baseline during either the histamine iontophoresis or the direct current stimulation experimental conditions. However, in the fifth minute of treatment systolic blood pressure during histamine iontophoresis was significantly lower when compared with the responses during direct current stimulation. Apart from this finding no significant difference in blood pressure and heart rate responses before, during or after treatment was recorded.

The statistically significant finding

Table5.
Untoward reactions during histamine iontophoresis treatment (N = 15).

Compliant	Frequency	% of subjects
During treatment		
Burning sensation	15	100
Immediately after treatment		
Dizziness	1	6.7
Headache	1	6.7
"Heaviness of the lower limbs"	2	13.4
24 hours post treatment		
Scalding	1	6.7
Itching	7	46.7
Wealing	4	26.8

obtained for the systolic blood pressure during the fifth minute of treatment could be attributed to chance because of lack of concordance with the findings in the other time frames during treatment and for the other variables measured. The findings suggest that local administration of histamine dihydrochloride (1 per cent concentration) into the skin by direct current for 20 minutes did not appreciably alter the cardiovascular functioning. The findings did not support the hypothesis of the study. It is possible that a higher concentration of the drug applied for a longer duration may significantly affect the cardiovascular system. This speculation is based on the fact that the number of ions that cross the skin barrier is dependent on 1) the current density of the active electrode, 2) duration of the treatment, and 3) concentration of the ions in the solution (Boone 1981, Cummings 1987, Kahn 1983).

The 20 minute treatment duration adopted in this study is in line with protocols recommended in the literature (Abramson et al 1967, Hayes 1979, Kahn 1983), however, the concentration of the histamine ion in the gel (1:100) that was used is higher than the concentration (1:10,000 fresh solution) used by Abramson et al 1967). Using the same dosage of histamine (1 per cent) as recommended by Hayes (1979) in a clinical setting, the present authors have noted successful enhancement to the healing of recalcitrant ulcers.

Many previous studies have evaluated the effect of subcutaneous administration of histamine on peripheral blood flow and oxygen uptake. On reviewing the literature, Abramson et al (1967) concluded that the findings of the various studies were contradictory. These authors cited five studies that reported a marked increase in basal metabolism and two other investigations that observed a decrease or no change in metabolism following intravenous injection of histamine. In addition, they cited two other studies that revealed "that histamine when applied by ion transfer to the upper extremities consistently produced a marked increase in local circulation". (Abramson et al 1967, p 583 - 591) In their own study, Abramson et al (1967) found an increase in blood flow within several minutes following histamine iontophoresis. The increase in blood flow continued throughout the 20 minutes of the treatment and for 60 minutes into the recovery period. Fifteen of the 16 subjects (94 per cent) in their study showed a fall in oxygen uptake within five minutes following histamine iontophoresis. Thereafter, the oxygen uptake either continued to remain below the baseline or rise above it slightly (Abramson et al 1967). No previous study has systematically monitored the blood pressure and heart rate during histamine iontophoresis, consequently direct comparison of the present results with previous studies is not feasible.

Clinical Implications

The absolute blood pressure and heart rate responses observed in this study were relatively small. However, the amount of histamine absorbed into the systemic circulation during the treatment was enough to cause some untoward reactions like dizziness and headache (Table 5). The findings of no statistically significant changes in cardiovascular functioning following both histamine iontophoresis and electrical stimulation treatments should be interpreted with caution. The findings may not be extrapolated directly to patients since healthy subjects were employed in the present study. Older patients and individuals with cardiorespiratory diseases may respond differently. The untoward reactions observed in the present study are consistent with previous anecdotal reports (Abramson et al 1967, Boone 1987, Cummings 1987, Hayes 1979). Subjective evaluation of the symptoms concomitant with histamine iontophoresis suggests that individuals react differently to histamine. Differences in skin sensitivity, unequal distribution of pressure over the electrodes and uneven application of the histamine gel may have accounted for the variability in the local reactions obtained in this study.

It is plausible that some of the local side effects experienced in this study may be avoided if a fresh solution of histamine dihydrochloride was utilized. Similarly, the cardiovascular responses during treatment may be different if fresh solution was employed because of the possibility of enhanced conductivity. These speculations could be investigated in follow-up studies. From a practical perspective, histamine

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iontophoresis using fresh solution medium has limited application since only the limbs can be treated with the procedure. Gel was employed in this investigation since many indolent ulcers are located on the back, sacrum and thigh, all of which are difficult areas to treat using fresh solution medium.

To determine the suitability of patients for histamine iontophoresis treatment, physical therapists are urged to question patients about any previous history of skin reaction (eg itching) following histamine injection; history of dizziness, fainting, or chronic headache, and any history of hypotension. It is expected that patients with these precipitating condition will produce exaggerated responses. Therefore, it is recommended that the cardiovascular responses and dermal reaction of such patients should be closely monitored before, during and after histamine iontophoresis.

Areas for further research

Some of the local reactions observed in this study may be attributed to the variability in the texture of the subjects' skin. Follow-up studies should carry out skin sensitivity tests over the treatment area. Prior to treatment, the skin should be well moistened to improve conductivity. It is possible that washing of the skin after treatment may reduced some of the local post treatment side effects such as scalding, itching and weal formation.

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